

# Type 2 Diabetes in a Time of Change—A Tide of Good News

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Type 2 diabetes has been definitively characterized as one of the most physiologically complex and heterogeneous metabolic known diseases. The extraordinary depth of knowledge that has been achieved regarding the pathophysiology has helped to stimulate an explosive array of therapeutic regimens and monitoring tools for improving outcomes in this disease. Indeed, the clinical narrative about ‘control’ of diabetes has shifted markedly in the last two years, away from a focus on glucose-mediated vascular complications to defining diabetes control as cardiovascular risk reduction and end organ protection. The new tools for management coupled with new pathophysiologic insights have brought a tide of good news for the millions of people living with type 2 diabetes.

## Keywords

Ominous octet, complex pathophysiology, complementary combination therapy, glucose control

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It hardly seems possible that only 21 years ago, the most exciting concept in type 2 diabetes (T2D) was the contribution of peripheral insulin resistance to disease pathophysiology, and the most important new tool to address this defect was the biguanide, metformin. The dominant conceptualization of the underlying defects accounting for the hyperglycemia of T2D had been introduced by Ralph DeFronzo several years earlier in his Lilly lecture as the ‘triumvirate’ of T2D pathophysiology.<sup>1</sup> The availability of metformin as a treatment tool to address insulin resistance greatly strengthened the ability of clinicians to fashion treatment regimens that appeared to align with the underlying disease process. The excitement generated by metformin has certainly been justified by its performance as foundation therapy for the vast majority of patients with T2D, with its effects on glucose and beyond.<sup>2</sup> This was a good news period for T2D. However, what we have witnessed over the last decade must be considered transformational in both our understanding of the underlying pathology of T2D and the tools that have been developed for its treatment and monitoring.

First, our understanding of the defects that drive the hyperglycemia of T2D has been greatly expanded to a more extensive spectrum of defects contributing to hyperglycemia in T2D, prompted by DeFronzo’s introduction of the ‘Ominous Octet’.<sup>3</sup> Indeed, this construct of diabetes initiated a break from the ‘stepped care’ approach to treatment to a more physiological algorithm for making treatment decisions. This alternate approach encourages earlier use of complementary combination therapy and offers a more rational approach that may provide better long-term effects. This approach has gained more traction in recent years, with the emergence of several new developments that offer good news for T2D.

Perhaps the most significant advance has been the availability of a broad spectrum of safe, efficacious newer agents that further expand the physiological targets for treatment of T2D, with complementary actions in their mechanisms.<sup>4</sup> This advance is important because these agents have proven to be effective in improving glucose control, while offering benefits for other cardiometabolic risk factors known to have significant impact on the increased coronary heart disease (CHD) mortality of T2D.<sup>5</sup> Thus, in contrast to the fear that such drugs might produce cardiovascular harm in attempts to better control T2D, these newer agents have proven to be not only safe,<sup>6–10</sup> but recently, we have seen evidence of cardiovascular protection in trials using the sodium-glucose transporter-2 (SGLT-2) inhibitor empagliflozin, with the GLP-1 receptor agonists liraglutide<sup>11</sup> and semaglutide,<sup>12</sup> and a similar effect has been seen with bromocriptine-QR.<sup>13</sup> These results have dramatically changed the narrative from a largely unfounded fear of using newer agents to treat T2D<sup>14</sup> to a view that indeed it may be time to realistically pursue reduced cardiovascular events and mortality as outcome measures in diabetes care, especially if the results reported to date prove to represent class effects for many of these agents (that is, the SGLT-2 inhibitors).

Earlier, intensive treatment will increasingly be more appealing since the newer agents generally present little risk of hypoglycemia unless they are used with sulfonylureas (SFUs) or insulin, and have complementary actions with most of the known treatments, allowing for more flexibility and frequent use of combination regimens. The glucagon-like peptide (GLP)-1 receptor agonists (RAs) provide a rational, effective alternative to insulin as the first injectable, and they combine effectively with insulin for improved glucose control, with lower weight gain and less hypoglycemia. They offer tremendous dosing flexibility, which may soon extend treatment options from twice-daily (BID), once daily, or once weekly to once every six to 12 months with the exenatide-containing implantable subcutaneous minipump.<sup>15</sup> Likewise, the newer insulins provide for exceptional flexibility in dosing schedule with the least biologic variability ever encountered. Moreover, given the user-friendly delivery devices now available for the GLP-1s and for the insulins, plus the abundance of once-daily OADs, the likelihood of increased adherence or persistence of effective therapy grows more probable, further enhancing the likelihood of better long-term outcomes. This is indeed a tide of good news for T2D.

Finally, the advent of breakthrough technology for continuous glucose monitoring (CGM) holds tremendous promise for T2D in addition to its clear advantages for type 1 diabetes. While the newer treatments in T2D present fewer risks for hypos, it will remain important for patients to accurately assess their timing and patterns of response to therapy, using newer, more physiologically relevant metrics such as glucose ‘time in range’ (TIR). Monitors such as those that store data for periods of up to two weeks, and require no finger-stick calibration represent important steps toward facilitating heightened self-management and persistence of therapy in T2D. This technology may also hold the promise of allowing more definitive assessment of the onset and course of prediabetes by providing real-time, long-term patterns of blood glucose patterns in the high risk, versus the ‘snapshots’ of fasting plasma glucose, postprandial glucose, or even the less-than-ideal average blood glucose, reflected by hemoglobin A1c. Truly, the combination of deeper insights into disease causation, access to safer, targeted, and complementary treatments, plus simpler, but more effective regimens, with improved delivery devices and monitoring systems signal a tide of good news for T2D, with more to come! □

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